09/148234
AM # 20

6/14/01

1. Document ID: US 6184037 B1

L7: Entry 1 of 24

File: USPT

Feb 6, 2001

US-PAT-NO: 6184037
DOCUMENT-IDENTIFIER: US 6184037 B1
TITLE: Chitosan related compositions and methods for delivery of nucleic acids and
oligonucleotides into a cell
DATE-ISSUED: February 6, 2001

US-CL-CURRENT: 435/455; 514/44, 514/55, 536/20, 536/23.1

APPL-NO: 8/ 850597
DATE FILED: May 2, 1997

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATIONS This application claims the benefit of Mumper and
Rolland, U.S. Provisional Application 60/018,342, entitled "Chitosan Related Compositions and
Methods for Delivery of Nucleic Acids and Oligonucleotides into a Cell", filed May 17, 1996. This
application is also related to Rolland and Mumper, U.S. patent application Ser. No. 08/372,213
entitled, "Formulated Nucleic Acid Compositions and Methods of Administering the Same for Gene
Therapy," filed Jan. 13, 1995. These applications are hereby incorporated herein by reference in
their entireties, including any drawings and figures.

IN: Rolland; Alain, Mumper; Russell J.

AB: Compositions of chitosan-based compounds and nucleic acid or oligonucleotide
which are capable of delivery to a cell. Methods of preparation of the compositions. Methods
of administering the compositions in vitro to cells in culture or in vivo to an organism.

L7: Entry 1 of 24

File: USPT

Feb 6, 2001

DOCUMENT-IDENTIFIER: US 6184037 B1
TITLE: Chitosan related compositions and methods for delivery of nucleic acids and
oligonucleotides into a cell

DEPR:
Nonlimiting examples of genes expressing the following growth factors which can be delivered to
these cell types are Insulin, Insulin-Like Growth Factor-1, Insulin-Like Growth Factor-2,
Epidermal Growth Factor, Transfecting Growth Factor-.alpha., Transfecting Growth Factor-.beta.,
Platelet Derived Growth Factor, Acidic Fibroblast Growth Factor, Basic Fibroblast Growth Factor,
Bone Derived Growth Factors, Bone Morphogenetic Protein, Cartilage Induction Factor, Estradiol,
and Growth Hormone. All of these factors have a positive effect on the proliferation of
osteoblasts, the related stem cells, and chondrocytes. As a result, BMP or CIF can be used as
conjugates to deliver genes that express these growth factors to the target cells by the
intravenous injection of the nucleic acid/chitosan compositions of the present invention. Using
the nucleic acid described above in the chitosan-based compositions of the present invention with
the use of specific ligands for the delivery of nucleic acid to bone cells provides treatment of
diseases and abnormalities that affect bone tissues.

2. Document ID: US 6143037 A

L7: Entry 2 of 24

File: USPT

Nov 7, 2000

US-PAT-NO: 6143037
DOCUMENT-IDENTIFIER: US 6143037 A
TITLE: Compositions and methods for coating medical devices
DATE-ISSUED: November 7, 2000

US-CL-CURRENT: 424/422; 427/2.1, 435/6, 514/44

APPL-NO: 8/ 662341
DATE FILED: June 12, 1996

IN: Goldstein; Steven, Levy; Robert J., Labhasetwar; Vinod, Bonadio; Jeffrey F.

AB: Compositions and methods for coating medical devices with pharmaceutical agents
and devices coated with the compositions. The coated devices provide controlled or sustained
release of pharmaceutical agents for the treatment of wounds or disease.

L7: Entry 2 of 24

File: USPT

Nov 7, 2000

DOCUMENT-IDENTIFIER: US 6143037 A
TITLE: Compositions and methods for coating medical devices

DEPR:
This aspect of the invention is based, in part, on the discovery that proliferating repair cells
involved in the wound healing process are surprisingly efficient at taking up, and optionally
expressing, nucleic acids (copending attorney docket no. 8464-007-999, filed Apr. 8, 1996). These
repair cells, which are normally difficult to efficiently transfect both in vitro and in vivo,
are extremely efficient at taking up and expressing nucleic acids when induced to proliferate by
the wound healing process. The repair cells migrate to a site of tissue injury, infiltrate
matrices containing nucleic acids placed at the injury and take up and express the nucleic acids.
For example, a collagen sponge containing plasmid DNA encoding mouse BMP-4 (an osteoconductive
factor normally expressed by progenitor cells during fracture repair) placed within a 5 mm
osteotomy in rats was found to promote bone growth across the gap (id).

3. Document ID: US 6077987 A

L7: Entry 3 of 24

File: USPT

Jun 20, 2000

US-PAT-NO: 6077987
DOCUMENT-IDENTIFIER: US 6077987 A
TITLE: Genetic engineering of cells to enhance healing and tissue regeneration
DATE-ISSUED: June 20, 2000

US-CL-CURRENT: 623/23.72; 424/422, 424/423, 424/93.21, 623/23.57, 623/23.6

APPL-NO: 8/ 923718
DATE FILED: September 4, 1997

IN: Breitbart; Arnold S., Grande; Daniel S., Mason; James M.

AB: A method for enhancing and/or increasing the efficiency of repair of tissues, primarily bone or cartilage, using genetically engineered cells has been developed. In the preferred embodiment, mesenchymal stem cells are isolated from periosteum tissue, and transfected with the gene encoding a growth factor for the particular cell type to be repaired. For example, for repair of bone, a gene (or genes) encoding bone morphogenic protein is transfected into periosteal cells. The transfected periosteal cells then express the bone morphogenic protein in culture to promote bone repair as a function of the expressed bone morphogenic protein. Cells can be transfected using any appropriate means, including viral vectors, as shown by the example, chemical transfectants, or physico-mechanical methods such as electroporation and direct diffusion of DNA. Genes can encode any useful protein, for example, a specific growth factor, morphogenesis factor, a structural protein, or a cytokine which enhances the temporal sequence of wound repair, alters the rate of proliferation, increases the metabolic synthesis of extracellular matrix proteins, or directs phenotypic expression in endogenous cell populations. Representative genes encoding proteins include bone growth factor genes, cartilage growth factor genes, nerve growth factor genes, and general growth factors important in wound healing, such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF-1), epidermal growth factor (EGF), basic fibroblast growth factor (FGF), endothelial derived growth supplement.

L7: Entry 3 of 24
File: USPT
Jun 20, 2000

DOCUMENT-IDENTIFIER: US 6077987 A
TITLE: Genetic engineering of cells to enhance healing and tissue regeneration

BSPR:
Preferred examples for bone repair and/or treatment of osteoporosis uses periosteal or other mesenchymal stem cells or osteocytes/osteoblasts transfected with bone growth factor genes such as bone morphogenetic protein (BMP) family genes, including BMP 2-15; for cartilage repair uses periosteal cells or chondrocytes transfected with cartilage growth factor genes such as transforming growth factor-.beta. (TGF-.beta.) and cartilage growth factor (CGF); for wound healing uses dermal or epidermal cells transfected with growth factor genes such as platelet derived growth factor (PDGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF), fibroblast growth factor (FGF), endothelial derived growth supplement (EDGS), or insulin-like growth factor (IGF); for nerve repair (central and/or peripheral) uses neural cells and neural support cells transfected with nerve growth factor (NGF) gene.

ORPL:
Hollnagel, et al, "Parathyroid Hormone (PTH) and PTH/PTHRP-Receptor Mediated Stimulation of Osteochondrogenic Development in BMP-Transfected C3H10T1/2 Mesenchymal Progenitor Cells," Calcified Tissue International 56(5): 430 (1995).

4. Document ID: US 6048964 A

L7: Entry 4 of 24
File: USPT
Apr 11, 2000

US-PAT-NO: 6048964
DOCUMENT-IDENTIFIER: US 6048964 A
TITLE: Compositions and therapeutic methods using morphogenic proteins and stimulatory factors
DATE-ISSUED: April 11, 2000

US-CL-CURRENT: 530/350; 435/235.1, 435/252.3, 435/320.1, 435/325, 435/375, 435/69.1, 530/300, 536/23.1

APPL-NO: 8/ 570752
DATE FILED: December 12, 1995

IN: Lee; John C., Yeh; Lee-Chuan C.

AB: The present invention provides pharmaceutical compositions comprising a morphogenic protein stimulatory factor (MPSF) for improving the tissue inductive activity of morphogenic proteins, particularly those belonging to the BMP protein family. Methods for improving the tissue inductive activity of a morphogenic protein in a mammal using those compositions are provided. This invention also provides implantable morphogenic devices comprising a morphogenic protein and a MPSF disposed within a carrier, that are capable of inducing tissue formation in allogeneic and xenogeneic implants. Methods for inducing local tissue formation from a progenitor cell in a mammal using those devices are also provided. A method for accelerating allograft repair in a mammal using morphogenic devices is provided. This invention also provides a prosthetic device comprising a prosthesis coated with a morphogenic protein and a MPSF, and a method for promoting in vivo integration of an implantable prosthetic device to enhance the bond strength between the prosthesis and the existing target tissue at the joining site. Methods of treating tissue degenerative conditions in a mammal using the pharmaceutical compositions are also provided.

L7: Entry 4 of 24
File: USPT
Apr 11, 2000

DOCUMENT-IDENTIFIER: US 6048964 A
TITLE: Compositions and therapeutic methods using morphogenic proteins and stimulatory factors

DEPR:
In one preferred embodiment of this invention, the morphogenic protein whose activity may be stimulated by the presence of a MPSF comprises a pair of subunits disulfide bonded to produce a dimeric species, wherein at least one of the subunits comprises a recombinant polypeptide belonging to the BMP protein family. The dimeric species may be a homodimer or heterodimer and is capable of inducing cell proliferation and/or tissue formation when accessible to a progenitor cell in the mammal. The progenitor cell may be induced to form one or more tissue types pereferably selected from the group consisting of endochondral or intramembranous bone, cartilage, tendon/ligament-like tissue, neural tissue and other organ tissue types, including kidney tissue.

5. Document ID: US 6034062 A

L7: Entry 5 of 24
File: USPT
Mar 7, 2000

US-PAT-NO: 6034062
DOCUMENT-IDENTIFIER: US 6034062 A
TITLE: Bone morphogenetic protein (BMP)-9 compositions and their uses
DATE-ISSUED: March 7, 2000

US-CL-CURRENT: 514/12; 530/350, 530/399, 930/120

APPL-NO: 8/ 815652
DATE FILED: March 13, 1997

IN: Thies; R. Scott, Song; Jeffrey J.

AB: Purified Bone Morphogenetic Protein (BMP)-9 proteins and processes for producing them are disclosed. The proteins may be used in the treatment of bone and cartilage defects and in wound healing and related tissue repair, and in hepatic growth and function.

L7: Entry 5 of 24
File: USPT
Mar 7, 2000

DOCUMENT-IDENTIFIER: US 6034062 A
TITLE: Bone morphogenetic protein (BMP)-9 compositions and their uses

DEPR:
Human BMP-9 may be produced by culturing a cell transformed with a DNA sequence comprising nucleotide #124 to #453 as shown in SEQ ID NO:8 and recovering and purifying from the culture medium a protein characterized by the amino acid sequence of SEQ ID NO:9 from amino acid #1 to amino acid #110 substantially free from other proteinaceous materials with which it is co-produced. For production in mammalian cells, the DNA sequence further comprises a DNA sequence encoding a suitable propeptide 5' to and lined in frame to the nucleotide sequence encoding the mature BMP-9-related polypeptide. The propeptide may be the native BMP-9-related propeptide, or may be a propeptide from another protein of the TGF-.beta. superfamily. BMP-9 proteins may be characterized by the ability to induce the formation of cartilage. BMP-9 proteins may be further characterized by the ability to induce the formation of bone. BMP-9 proteins may be further characterized by the ability to demonstrate cartilage and/or bone formation activity in the rat bone formation assay described below. BMP-9 proteins may be further characterized by the ability to demonstrate effects upon the growth and/or differentiation of embryonic cells and/or stem cells. The proteins or compositions of the present invention may also be useful for treating cell populations, such as embryonic cells or stem cell populations, to enhance or enrich the growth and/or differentiation of the cells.

6. Document ID: US 6027917 A

L7: Entry 6 of 24
File: USPT
Feb 22, 2000

US-PAT-NO: 6027917
DOCUMENT-IDENTIFIER: US 6027917 A
TITLE: Bone morphogenetic protein (BMP)-17 and BMP-18 compositions
DATE-ISSUED: February 22, 2000

US-CL-CURRENT: 435/69.1; 435/252.3, 435/325, 536/23.5, 536/23.51

APPL-NO: 8/ 987904
DATE FILED: December 10, 1997

IN: Celeste; Anthony J., Murray; Beth L.

AB: Purified BMP-17 and BMP-18 proteins and processes for producing them are disclosed. DNA molecules encoding the BMP-17 and BMP-18 proteins are also disclosed. The proteins may be used in the treatment of bone, cartilage, other connective tissue defects and disorders, including tendon, ligament and meniscus, in wound healing and related tissue repair, as well as for treatment of disorders and defects to tissues which include epidermis, nerve, muscle, including cardiac muscle, and other tissues and wounds, and organs such as liver, lung, epithelium, brain, spleen, cardiac, pancreas and kidney tissue. The proteins may also be useful for the induction of growth and/or differentiation of undifferentiated embryonic and stem cells.

L7: Entry 6 of 24
File: USPT
Feb 22, 2000

DOCUMENT-IDENTIFIER: US 6027917 A
TITLE: Bone morphogenetic protein (BMP)-17 and BMP-18 compositions

BSPR:

It is expected that other species, particularly human, have DNA sequences homologous to human
BMP-17 and BMP-18 protein. The invention, therefore, includes methods for obtaining the DNA
sequences encoding human BMP-17 and BMP-18 proteins, the DNA sequences obtained by those methods,
and the human proteins encoded by those DNA sequences. This method entails utilizing the human
BMP-17 and BMP-18 nucleotide sequences or portions thereof to design probes to screen libraries
for the corresponding gene from other species or coding sequences or fragments thereof from using
standard techniques. Thus, the present invention may include DNA sequences from other species,
which are homologous to human BMP-17 and BMP-18 proteins and can be obtained using the human
BMP-17 and/or BMP-18 sequences. The present invention may also include functional fragments of
the human BMP-17 and BMP-18 proteins, and DNA sequences encoding such functional fragments, as
well as functional fragments of other related proteins. The ability of such a fragment to
function is determinable by assay of the protein in the biological assays described for the assay
of the BMP-17 and BMP-18 proteins. DNA sequences encoding the complete mature human BMP-17 (SEQ
ID NO: 1 and BMP-18 protein (SEQ ID NO:3) and the corresponding amino acid sequences (SEQ ID NO:2
and 4, respectively) are set forth herein. The BMP-17 and BMP-18 proteins of the present
invention, such as human BMP-17 and BMP-18, may be produced by culturing a cell transformed with
the correlating DNA sequence, such as the human BMP-17 and BMP-18 DNA sequence, and recovering
and purifying protein, such as BMP-17 or BMP-18, from the culture medium. The purified expressed
protein is substantially free from other proteinaceous materials with which it is co-produced, as
well as from other contaminants. The recovered purified protein is contemplated to exhibit
cartilage and/or bone and/or connective tissue formation activity. Thus, the proteins of the
invention may be further characterized by the ability to demonstrate cartilage and/or bone and/or
other connective tissue formation activity in the rat bone formation assay described below.
BMP-17 and BMP-18 proteins may be further characterized by the ability to demonstrate effects
upon the growth and/or differentiation of embryonic cells and/or stem cells. Thus, the proteins
or compositions of the present invention may also be characterized by their ability to enhance or
enrich the growth and/or differentiation of the cells.

7. Document ID: US 6001654 A

L7: Entry 7 of 24 File: USPT Dec 14, 1999

US-PAT-NO: 6001654
DOCUMENT-IDENTIFIER: US 6001654 A
TITLE: Methods for differentiating neural stem cells to neurons or smooth muscle cells using
TGT-.beta. super family growth factors
DATE-ISSUED: December 14, 1999

US-CL-CURRENT: 435/377; 435/325, 435/352, 435/353, 435/368, 435/375

APPL-NO: 8/ 846028

DATE FILED: April 25, 1997

PARENT-CASE:
This is a continuation in part of U.S. patent application Ser. No. 08/188,286 filed Jan. 28,
1994, now U.S. Pat. No. 5,654,183, which is a continuation-in-part of PCT Application No.
PCT/US93/07000 filed Jul. 26, 1993, published Feb. 3, 1994, as WO 94/02593, which is a
continuation-in-part of U.S. patent application Ser. No. 07/969,088 filed Oct. 29, 1992, now
abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 07/920,617, filed
Jul. 27, 1992, now abandoned. This application also claims benefit under 35 U.S.C. .sctn. 119(e)
U.S. provisional patent application No. 60/044,797, filed Apr. 24, 1997.

IN: Anderson; David J., Shah; Nirao M.

AB: Method for producing a population of mammalian neurons and/or smooth muscle cells
comprising contacting at least one mammalian neural stem cell with a culture medium
containing one or more growth factors from the TGF-.beta. super family and detecting the
differentiation of stem cell to a population of neurons or smooth muscle cells.

L7: Entry 7 of 24 File: USPT Dec 14, 1999

DOCUMENT-IDENTIFIER: US 6001654 A
TITLE: Methods for differentiating neural stem cells to neurons or smooth muscle cells using
TGT-.beta. super family growth factors

DEPR:
As used herein, the term "growth factors from the TGF-.beta. superfamily" means growth factors
related to transforming growth factor beta-1 ("TGF.beta.-1"). Such TGF-.beta. superfamily growth
factors may or may not exert a similar biological effect to TGF.beta.-1, the prototypic member of
the TGF-.beta. superfamily. In recombinant TGF-.beta.1 ("rTGF-.beta.1") virtually all neural
crest stem cell colonies differentiate to SM cells under specified culture conditions. Shah et
al.(1996) Cell 85:331-343. TGF.beta.2 and TGF.beta.3 yielded similar results as TGF.beta.1. Shah
et al.(1996) Cell 85:331-343, data not shown. By way of example, members of the TGF-.beta.
superfamily of growth factors include but are not limited to naturally occurring analogues (e.g.
TGF.beta.-2, .beta.-3, .beta.4),and any known synthetic or natural analogues of TGF.beta.-1 in
addition to related growth factors exemplified by bone morphogenic proteins 2 and 4 ("BMP-2" and
"BMP-4"). These compounds can be purified from natural sources or may be produced by recombinant
DNA techniques and may or may not be substantially pure. Variants and fragments retaining the
property of causing differentiation are included in the definition of the members of this
superfamily.

8. Document ID: US 5994131 A

L7: Entry 8 of 24

File: USPT

Nov 30, 1999

US-PAT-NO: 5994131
DOCUMENT-IDENTIFIER: US 5994131 A
TITLE: Morphogenic protein screening method
DATE-ISSUED: November 30, 1999

US-CL-CURRENT: 435/354; 435/325

APPL-NO: 8/ 912088
DATE FILED: August 15, 1997

PARENT-CASE:
This is a divisional of application U.S. Ser. No. 08/451,953 filed on May 26, 1995, U.S. Pat. No.
5,741,641, which is a continuation of U.S. Ser. No. 08/278,729 filed on Jul. 20, 1994, U.S. Pat.
No. 5,650,276, which is a continuation of U.S. Ser. No. 07/938,021 filed on Aug. 28, 1992,
abandoned, which is a continuation-in-part of U.S. Ser. Nos. 07/752,861, abandoned, and
07/752,764, abandoned, both filed on Aug. 30, 1991 and both of which are continuations-in-part of
U.S. Ser. No. 667,274 filed Mar. 11, 1991, abandoned.

IN: Smart; John E., Oppermann; Hermann, Ozkaynak; Engin, Kuberasampath; Thangavel,
Rueger; David C., Pang; Roy H. L., Cohen; Charles M.

AB: Disclosed is a method of screening candidate compounds for the ability to
modulate the level of morphogenic protein in mammalian system. The method includes
determining a parameter indicative of the level of production of a morphogenic in a cell
culture known to produce the morphogen, incubating a candidate compound with the culture for
a time sufficient to allow the compound to affect the production of the morphogenic protein,
and then assaying the culture again to detect a change in the level of morphogenic protein
production.

L7: Entry 8 of 24

File: USPT

Nov 30, 1999

DOCUMENT-IDENTIFIER: US 5994131 A
TITLE: Morphogenic protein screening method

DEPR:
The invention is based on the discovery of a family of structurally related morphogenic proteins
(BMPs), also called osteogenic proteins (OPs), and more particularly that various of these
proteins play an important role, not only in embryogenesis, but also in tissue and organ
maintenance and repair in juvenile and adult mammals. Morphogenic proteins which have been
identified include BMP 2, 3, 4, 5, 6, OP-1 and OP-2 (murine and human), Vgr-1, Vgl, DPP, GDF-1,
CMBP-2A, CMBP-2B, 60A, and the inhibin/activin class of proteins. Other recombinant proteins
include COP1, COP3, COP4, COP5, COP7, and COP16. While, as explained herein, the morphogen have
significant homologies and similarities in structure, it is hypothesized that variants within the
morphogenic protein genes may have specific roles in specific tissue involving, for example,
stimulation of progenitor cell multiplication, tissue specific or tissue preferred phenotype
maintenance, and/or stimulation or modulation of the rate of differentiation, growth or
replication of tissue cells characterized by high turnover. The effect on the long-term
physiology, maintenance and repair of particular tissues by particular species of the morphogens
is currently unknown in any significant detail. However, methods useful in determining which
particular tissues express which particular morphogen(s), and for finding changes which stimulate
or depress morphogen expression in vivo, would enable discovery and development of strategies for
therapeutic treatment of a large number of diseased states, and provide drugs designed to
implement the strategy.

9. Document ID: US 5986056 A

L7: Entry 9 of 24

File: USPT

Nov 16, 1999

US-PAT-NO: 5986056
DOCUMENT-IDENTIFIER: US 5986056 A
TITLE: Chordin compositions
DATE-ISSUED: November 16, 1999

US-CL-CURRENT: 530/350; 435/69.1

APPL-NO: 9/ 130032
DATE FILED: August 4, 1998

PARENT-CASE:
This application is a divisional of U.S. Ser. No. 08/749,169, U.S. Pat. No. 5,846,770 filed Nov.
14, 1996, which application is a continuation-in-part of U.S. Ser. No. 08/343,760, filed Nov. 22,
1994, and now issued as U.S. Pat. No. 5,679,783.

IN: LaVallie; Edward R., Racie; Lisa A., DeRobertis; Edward M.

AB: Purified chordin proteins and processes for producing them are disclosed. DNA
molecules encoding the chordin proteins are also disclosed. The proteins may be used in the
treatment of bone, cartilage, other connective tissue defects and disorders, including
tendon, ligament and meniscus, in wound healing and related tissue repair, as well for
treatment of disorders and defects to tissue which include epidermis, nerve, muscle,
including cardiac muscle, and othe tissues and wounds, and organs such as liver, brain,
lung, cardiac, pancreas and kidney tissue. The proteins may also be useful for the induction
inhibition of growth and/or differentiation of undifferentiated embryonic and stem cells.
The proteins may be complexed with other proteins, particularly members of the transforming
growth factor-beta superfamily of proteins.

L7: Entry 9 of 24

File: USPT

Nov 16, 1999

DOCUMENT-IDENTIFIER: US 5986056 A
TITLE: Chordin compositions

BSPR:
It is expected that other species, particularly human, have DNA sequences homologous to human
chordin protein. The invention, therefore, includes methods for obtaining the DNA sequences
encoding human chordin protein, the DNA sequences obtained by those methods, and the human
protein encoded by those DNA sequences. This method entails utilizing the human chordin protein
nucleotide sequence or portions thereof to design probes to screen libraries for the
corresponding gene from other species or coding sequences or fragments thereof from using
standard techniques. Thus, the present invention may include DNA sequences from other species,
which are homologous to human chordin protein and can be obtained using the human chordin
sequence. The present invention may also include functional fragments of the human chordin
protein, and DNA sequences encoding such functional fragments, as well as functional fragments of
other related proteins. The ability of such a fragment to function is determinable by assay of
the protein in the biological assays described for the assay of the chordin protein; for example
the BMP binding assays described in the examples. A DNA sequence encoding the complete mature
human chordin protein (SEQ ID NO: 1 and SEQ ID NO: 2) and the corresponding amino acid sequence
(SEQ ID NO: 3) are set forth herein. The chordin proteins of the present invention, such as human
chordin, may be produced by culturing a cell transformed with the correlating DNA sequence, such
as the human chordin DNA sequence of SEQ ID NO: 2, and recovering and purifying protein, such as
human chordin, from the culture medium. The purified expressed protein is substantially free from
other proteinaceous materials with which it is co-produced, as well as from other contaminants.
The recovered purified protein is contemplated to have the ability to bind to BMPs and hence to
exhibit effects on cartilage, bone and/or other connective tissue formation activity. Thus, the
proteins of the invention may be further characterized by the ability to demonstrate effects on
cartilage, bone and/or other connective tissue formation activity in bone and cartilage formation
and other assays described below. Chordin proteins may be further characterized by the ability to
demonstrate effects upon the growth and/or differentiation of embryonic cells and/or stem cells.
Thus, the proteins or compositions of the present invention may also be characterized by their
ability to enhance, enrich or otherwise influence the growth and/or differentiation of the cells.

APPL-NO: 8/ 289794
DATE FILED: August 12, 1994

IN: Long; Michael W., Mann; Kenneth G.

AB: Disclosed are methods, compositions and uses of bone precursor cells. Bone
precursor cells are cells which are not hematopietic and which can differentiate into
osteoblasts upon exposure to a bone growth factor and deposit calcium into the extracellular
matrix. In addition, methods of differentiating bone precursor cells into osteoblasts are
disclosed. Bone precursor cells are useful in the treatment of certain bone related
disorders and diseases such as, promoting fracture repair.

L7: Entry 10 of 24

File: USPT

Oct 26, 1999

DOCUMENT-IDENTIFIER: US 5972703 A
TITLE: Bone precursor cells: compositions and methods

DEPR:
Both cluster-forming, and colony-forming osteoprogenitor cells show an obligate requirement for
growth factors, and a differential responsiveness to bone-regulatory cytokines (FIG. 5). Both
progenitor cell types fail to develop in the absence osteogenic growth factors (media controls,
FIG. 5), whereas the addition of recombinant human growth factors known to regulate osteoblasts
(Urist et al., 1983; Hauschka et al., 1986; Noda et al., 1989; Rodan et al., 1989; and Wozney et
al., 1988) stimulates both cluster and colony formation. The colony-forming progenitor cells
respond equally well to TGF-.beta. and bFGF, generating approximately 40-60 colonies per 10.sup.5
cells (FIG. 5A). Likewise, 1,25-OH D3 and BMP-2 both stimulate colony forming cells, but to a
lesser degree than that seen with TGF-.beta. or bFGF. More mature progenitor cells respond best
to 1,25-OH vitamin D3 (vit. D3; values are negative logarithms of molarity), intermediately well
to both bone morphogenic protein (BMP-2; values are ng/mL) and transforming growth factor-.beta.
(IGF-.beta.; values are pM), but fail to respond to basic fibroblast growth factor (bFGF, values
are ng/mL). Bars labeled as "Media" are immune-adherent cells cultured in serum-free conditions
without the addition of exogenous growth factors.

10. Document ID: US 5972703 A

L7: Entry 10 of 24

File: USPT

Oct 26, 1999

US-PAT-NO: 5972703
DOCUMENT-IDENTIFIER: US 5972703 A
TITLE: Bone precursor cells: compositions and methods
DATE-ISSUED: October 26, 1999

US-CL-CURRENT: 435/372; 424/139.1, 424/141.1, 424/173.1, 435/325, 435/355, 435/366, 435/378,
530/388.2, 530/388.7, 530/389.6, 530/412, 530/413

11. Document ID: US 5965403 A

L7: Entry 11 of 24

File: USPT

Oct 12, 1999

US-PAT-NO: 5965403
DOCUMENT-IDENTIFIER: US 5965403 A
TITLE: Nucleic acids encoding bone morphogenic protein-16 (BMP-16)
DATE-ISSUED: October 12, 1999

US-CL-CURRENT: 435/69.4; 435/252.3, 435/320.1, 435/325, 435/69.1, 435/69.7, 536/23.1, 536/23.5,
536/23.51, 536/24.1

APPL-NO: 8/ 715202
DATE FILED: September 18, 1996

IN: Celeste; Anthony J., Murray; Beth L.

AB: Purified BMP-16 proteins and processes for producing them are disclosed. DNA molecules encoding the BMP-16 proteins are also disclosed. The proteins may be used in the treatment of bone, cartilage, other connective tissue defects and disorders, including tendon, ligament and meniscus, in wound healing and related tissue repair, as well as for treatment of disorders and defects to tissues which include epidermis, nerve, muscle, including cardiac muscle, and other tissues and wounds, and organs such as liver, lung, cardiac, pancreas and kidney tissue. The proteins may also be useful for the induction of growth and/or differentiation of undifferentiated embryonic and stem cells.

L7: Entry 11 of 24
File: USPT
Oct 12, 1999

DOCUMENT-IDENTIFIER: US 5965403 A
TITLE: Nucleic acids encoding bone morphogenic protein-16 (BMP-16)

BSPR:
It is expected that other species, particularly human, have DNA sequences homologous to human BMP-16 protein. The invention, therefore, includes methods for obtaining the DNA sequences encoding human BMP-16 protein, the DNA sequences obtained by those methods, and the human protein encoded by those DNA sequences. This method entails utilizing the human BMP-16 protein nucleotide sequence or portions thereof to design probes to screen libraries for the corresponding gene from other species or coding sequences or fragments thereof from using standard techniques. Thus, the present invention may include DNA sequences from other species, which are homologous to human BMP-16 protein and can be obtained using the human BMP-16 sequence. The present invention may also include functional fragments of the human BMP-16 protein, and DNA sequences encoding such functional fragments, as well as functional fragments of other related proteins. The ability of such a fragment to function is determinable by assay of the protein in the biological assays described for the assay of the BMP-16 protein. A DNA sequence encoding the complete mature human BMP-16 protein (SEQ ID NO:1) and the corresponding amino acid sequence (SEQ ID NO:2) are set forth herein. The BMP-16 proteins of the present invention, such as human BMP-16, may be produced by culturing a cell transformed with the correlating DNA sequence, such as the human BMP-16 DNA sequence, and recovering and purifying protein, such as BMP-16, from the culture medium. The purified expressed protein is substantially free from other proteinaceous materials with which it is co-produced, as well as from other contaminants. The recovered purified protein is contemplated to exhibit cartilage and/or bone and/or connective tissue formation activity. Thus, the proteins of the invention may be further characterized by the ability to demonstrate cartilage and/or bone and/or other connective tissue formation activity in the rat bone formation assay described below. BMP-16 proteins may be further characterized by the ability to demonstrate effects upon the growth and/or differentiation of embryonic cells and/or stem cells. Thus, the proteins or compositions of the present invention may also be characterized by their ability to enhance or enrich the growth and/or differentiation of the cells.

12. Document ID: US 5962427 A

L7: Entry 12 of 24
File: USPT
Oct 5, 1999

US-PAT-NO: 5962427
DOCUMENT-IDENTIFIER: US 5962427 A
TITLE: In vivo gene transfer methods for wound healing
DATE-ISSUED: October 5, 1999

US-CL-CURRENT: 514/44; 424/93.21, 435/320.1, 435/325, 435/455, 435/458, 536/24.5

APPL-NO: 8/ 631334
DATE FILED: April 12, 1996

PARENT-CASE:
This application is a Continuation-in-Part Application of PCT/US95/02251, filed Feb. 21, 1995 which is a Continuation-in-Part Application of U.S. Ser. No. 08/316,650, filed Sep. 30, 1994, which is a Continuation-in-Part Application of Ser. No. 08/199,780, filed Feb. 18, 1994.

IN: Goldstein; Steven A., Bonadio; Jeffrey

AB: The present invention relates to an in vivo method for specific targeting and transfer of DNA into mammalian repair cells. The transferred DNA may include any DNA encoding a therapeutic protein of interest. The invention is based on the discovery that mammalian repair cells proliferate and migrate into a wound site where they actively take up and express DNA. The invention further relates to pharmaceutical compositions that may be used in the practice of the invention to transfer the DNA of interest. Such compositions include any suitable matrix in combination with the DNA of interest.

L7: Entry 12 of 24
File: USPT
Oct 5, 1999

DOCUMENT-IDENTIFIER: US 5962427 A
TITLE: In vivo gene transfer methods for wound healing

DEPR:
Bone has a substantial capacity to regenerate following fracture. The complex but ordered fracture repair sequence includes hemostasis, clot dissolution, granulation tissue ingrowth, formation of a callus, and remodeling of the callus to an optimized structure (A. W. Ham., 1930, J. Bone Joint Surg. 12, 827-844). Cells participating in this process include platelets, inflammatory cells, fibroblasts, endothelial cells, pericytes, osteoclasts, and osteogenic progenitors. Recently, several peptide growth and differentiation factors have been identified

that appear to control cellular events associated with bone formation and repair (Erlebacher, A., et al., 1995, Cell 80, 371-378). Bone morphogenetic proteins (BMPs), for example, are soluble extracellular factors that control osteogenic cell fate: BMP genes are normally expressed by cultured fetal osteoblasts (Harris, S. E., et al., 1994, J. Bone Min. Res. 9, 389-394) and by osteoblasts during mouse embryo skeletogenesis (Lyons, K. M., et al., 1989, Genes Dev. 3, 1657-1668; Lyons, K. M., et al., 1990, Development 190, 833-844; Jones, M. C., et al., 1991, Development 111, 531-542), recombinant BMP proteins initiate cartilage and bone progenitor cell differentiation (Yamaguchi, A., et al., 1991, J. Cell Biol. 113, 681-687; Ahrens, M., et al., 1993, J. Bone Min. Res. 12, 871-880; Gitelman, S. E., et al., 1994, J. Cell Biol. 126, 1595-1609; Rosen, V., et al., 1994, J. Cell Biol. 127, 1755-1766), delivery of recombinant BMPs induce a bone formation sequence similar to endochondral bone formation (Wozney, J. M., 1992, Mol. Reprod. Dev. 32, 160-167; Reddi, A. H., 1994, Curr. Opin. Genet. Dev. 4, 737-744), and BMP-4 gene expression is unregulated early in the process of fracture repair (Nakase, T., et al., 1994, J. Bone Min. Res. 9, 651-659). Osteogenic protein-1, a member of a family of molecules related to the BMPs (Ozkaynak, E., et al., 1990, EMBO J. 9, 2085-2093), is capable of similar effects in vitro and in vivo (Sampath, T. K., et al., 1992, J. Biol. Chem. 267, 20352-20362; Cook, S. D., et al., (1994) J. Bone Joint Surg. 76-A, 827-838). TGF-.beta. has also been shown to stimulate cartilage and bone formation in vivo (Centrella, M., et al., 1994, Endocrine Rev. 15, 27-38; Sumner, D. R., et al., 1995, J. Bone Joint Surg. 77A, 1135-1147). Finally, parathyroid hormone (PTH) is an 84 amino acid hormone that raises the plasma and extracellular fluid Ca.sup.+2 concentration. In skeletal tissues, intermittent administration of a PTH fragment-possessing the structural requirements for biological activity (aa 1-34) produces a true anabolic effect: numerous in vivo and in vitro studies provide strong evidence that PTH1-34 administration in animals (including rats) results in uncoupled, high-quality bone formation due to a combined inhibitory effect on osteoclasts and stimulatory effect on osteogenic cells (Dempster, D. W., et al., 1993, Endocrine Rev. 14, 690-709). The PTH1-34 peptide is known to interact synergistically with BMP-4, which up-regulates the expression of functional cell surface PTH receptors in differentiating osteoblasts in vitro (Ahrens, M., et al., 1993, J. Bone Min. Res. 12, 871-880).

DEPR:
Having demonstrated that gap cells express functional enzymes following uptake of plasmid DNA from a matrix, we asked whether gene transfer could be used to modulate bone regeneration. We chose to overexpress BMP-4, an osteoinductive factor that normally is expressed by progenitor cells during fracture repair. A full length mouse BMP-4 CDNA was generated by PCR and subcloned into the pcDNA3 (Invitrogen) eukaryotic expression vector (FIG. 2). To specifically detect recombinant proteins, the 3' end of the BMP-4 coding sequence was modified by addition of a hemagglutinin (HA) epitope. Recombinant BMP-4 was expressed from this construct (pGAMI) using an in vitro transcription and translation protocol. Immunoprecipitation studies established the ability of the HA epitope to be recognized by an anti-HA polyclonal antibody. Biosynthesis of recombinant BMP-4 was evaluated following transient transfection of cultured 293T cells with PGAMI plasmid DNA. As demonstrated by immunoprecipitation, BMP-4 molecules were assembled into homodimers, secreted, and processed as expected. Taken together these results established that the HA-epitope was recognized by the anti-HA polyclonal antibody.

13. Document ID: US 5948428 A

L7: Entry 13 of 24 File: USPT Sep 7, 1999

US-PAT-NO: 5948428
DOCUMENT-IDENTIFIER: US 5948428 A
TITLE: Compositions and therapeutic methods using morphogenic proteins and stimulatory factors
DATE-ISSUED: September 7, 1999

US-CL-CURRENT: 424/426; 523/114, 523/115, 530/353

APPL-NO: 8/ 761468
DATE FILED: December 6, 1996

PARENT-CASE:
This application is a continuation-in-part of U.S. application Ser. No. 08/570,752, filed on Dec. 12, 1995.

IN: Lee; John C., Yeh; Lee-Chuan C.

AB: The present invention provides pharmaceutical compositions comprising a morphogenic protein stimulatory factor (MPSF) for improving the tissue inductive activity of morphogenic proteins, particularly those belonging to the BMP protein family. Methods for improving the tissue inductive activity of a morphogenic protein in a mammal using those compositions are provided. This invention also provides implantable morphogenic devices comprising a morphogenic protein and a MPSF disposed within a carrier, that are capable of inducing tissue formation in allogeneic and xenogeneic implants. Methods for inducing local tissue formation from a progenitor cell in a mammal using those devices are also provided. A method for accelerating allograft repair in a mammal using morphogenic devices is provided.
This invention also provides a prosthetic device comprising a prosthesis coated with a morphogenic protein and a MPSF, and a method for promoting in vivo integration of an implantable prosthetic device to enhance the bond strength between the prosthesis and the existing target tissue at the joining site. Methods of treating tissue degenerative conditions in a mammal using the pharmaceutical compositions are also provided.

L7: Entry 13 of 24 File: USPT Sep 7, 1999

DOCUMENT-IDENTIFIER: US 5948428 A
TITLE: Compositions and therapeutic methods using morphogenic proteins and stimulatory factors

DEPR:
In one preferred embodiment of this invention, the morphogenic protein whose activity may be
stimulated by the presence of a MPSF comprises a pair of subunits disulfide bonded to produce a
dimeric species, wherein at least one of the subunits comprises a recombinant polypeptide
belonging to the BMP protein family. The dimeric species may be a homodimer or heterodimer and is
capable of inducing cell proliferation and/or tissue formation when accessible to a progenitor
cell in the mammal. The progenitor cell may be induced to form one or more tissue types
preferably selected from the group consisting of endochondral or intramembranous bone, cartilage,
tendon/ligament-like tissue, neural tissue and other organ tissue types, including kidney tissue.

14. Document ID: US 5916870 A

L7: Entry 14 of 24

File: USPT

Jun 29, 1999

US-PAT-NO: 5916870
DOCUMENT-IDENTIFIER: US 5916870 A
TITLE: Compositions and therapeutic methods using morphogenic proteins and stimulatory factors
DATE-ISSUED: June 29, 1999

US-CL-CURRENT: 514/2; 514/21

APPL-NO: 9/ 158220
DATE FILED: September 22, 1998

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATIONS This application is a division of U.S. patent application
Ser. No. 09/027,873, filed Feb. 23, 1998, now pending, the entire disclosure of which is hereby
incorporated by reference; which is a division of U.S. patent application Ser. No. 08/570,752,
filed Dec. 12, 1995, now allowed.

IN: Lee; John C., Yeh; Lee-Chuan C.

AB: The present invention provides pharmaceutical compositions comprising a
morphogenic protein stimulatory factor (MPSF) for improving the tissue inductive activity of
morphogenic proteins, particularly those belonging to the BMP protein family. Methods for
improving the tissue inductive activity of a morphogenic protein in a mammal using those
compositions are provided. This invention also provides implantable morphogenic devices
comprising a morphogenic protein and a MPSF disposed within a carrier, that are capable of
inducing tissue formation in allogeneic and xenogeneic implants. Methods for inducing local
tissue formation from a progenitor cell in a mammal using those devices are also provided. A
method for accelerating allograft repair in a mammal using morphogenic devices is provided.
This invention also provides a prosthetic device comprising a prosthesis coated with a
morphogenic protein and a MPSF, and a method for promoting in vivo integration of an
implantable prosthetic device to enhance the bond strength between the prosthesis and the existing target tissue at the joining site. Methods of treating tissue degenerative
conditions in a mammal using the pharmaceutical compositions are also provided.

L7: Entry 14 of 24

File: USPT

Jun 29, 1999

DOCUMENT-IDENTIFIER: US 5916870 A
TITLE: Compositions and therapeutic methods using morphogenic proteins and stimulatory factors

DEPR:
In one preferred embodiment of this invention, the morphogenic protein whose activity may be
stimulated by the presence of a MPSF comprises a pair of subunits disulfide bonded to produce a
dimeric species, wherein at least one of the subunits comprises a recombinant polypeptide
belonging to the BMP protein family. The dimeric species may be a homodimer or heterodimer and is
capable of inducing cell proliferation and/or tissue formation when accessible to a progenitor
cell in the mammal. The progenitor cell may be induced to form one or more tissue types
pereferably selected from the group consisting of endochondral or intramembranous bone,
cartilage, tendon/ligament-like tissue, neural tissue and other organ tissue types, including
kidney tissue.

15. Document ID: US 5854207 A

L7: Entry 15 of 24

File: USPT

Dec 29, 1998

US-PAT-NO: 5854207
DOCUMENT-IDENTIFIER: US 5854207 A
TITLE: Compositions and therapeutic methods using morphogenic proteins and stimulatory factors
DATE-ISSUED: December 29, 1998

US-CL-CURRENT: 514/2; 514/21

APPL-NO: / 027873
DATE FILED: February 23, 1998

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATIONS This application is a division of U.S. patent application
Ser. No. 08/570,752, filed Dec. 12, 1995, now abandoned, the entire disclosure of which is hereby
incorporated by reference.

IN: Lee; John C., Yeh; Lee-Chuan C.

AB: The present invention provides pharmaceutical compositions comprising a
morphogenic protein stimulatory factor (MPSF) for improving the tissue inductive activity of
morphogenic proteins, particularly those belonging to the BMP protein family. Methods for
improving the tissue inductive activity of a morphogenic protein in a mammal using those
compositions are provided. This invention also provides implantable

morphogenic devices
comprising a morphogenic protein and a MPSF disposed within a carrier, that are capable of
inducing tissue formation in allogeneic and xenogeneic implants. Methods for inducing local
tissue formation from a progenitor cell in a mammal using those devices are also provided. A
method for accelerating allograft repair in a mammal using morphogenic devices is provided.
This invention also provides a prosthetic device comprising a prosthesis coated with a
morphogenic protein and a MPSF, and a method for promoting in vivo integration of an
implantable prosthetic device to enhance the bond strength between the prosthesis and the
existing target tissue at the joining site. Methods of treating tissue degenerative
conditions in a mammal using the pharmaceutical compositions are also provided.

L7: Entry 15 of 24

File: USPT

Dec 29, 1998

DOCUMENT-IDENTIFIER: US 5854207 A
TITLE: Compositions and therapeutic methods using morphogenic proteins and stimulatory factors

DEPR:
In one preferred embodiment of this invention, the morphogenic protein whose activity may be
stimulated by the presence of a MPSF comprises a pair of subunits disulfide bonded to produce a
dimeric species, wherein at least one of the subunits comprises a recombinant polypeptide
belonging to the BMP protein family. The dimeric species may be a homodimer or heterodimer and is
capable of inducing cell proliferation and/or tissue formation when accessible to a progenitor
cell in the mammal. The progenitor cell may be induced to form one or more tissue types
pereferably selected from the group consisting of endochondral or intramembranous bone,
cartilage, tendon/ligament-like tissue, neural tissue and other organ tissue types, including
kidney tissue.

16. Document ID: US 5846770 A

L7: Entry 16 of 24

File: USPT

Dec 8, 1998

US-PAT-NO: 5846770
DOCUMENT-IDENTIFIER: US 5846770 A
TITLE: DNA molecules encoding human chordin
DATE-ISSUED: December 8, 1998

US-CL-CURRENT: 435/69.1; 435/252.3, 435/320.1, 435/325, 435/69.7, 536/23.4, 536/23.5

APPL-NO: 8/749169
DATE FILED: November 14, 1996

PARENT-CASE:
This application is a continuation-in-part from Ser. No. 343,760, filed on Nov. 22, 1994, and
issued as U.S. Pat. No. 5,679,783.

IN: LaVallie; Edward R., Racie; Lisa A., DeRobertis; Edward M.

AB: Purified chordin proteins and processes for producing them are disclosed. DNA
molecules encoding the chordin proteins are also disclosed. The proteins may be used in the
treatment of bone, cartilage, other connective tissue defects and disorders, including
tendon, ligament and meniscus, in wound healing and related tissue repair, as well as for
treatment of disorders and defects to tissues which include epidermis, nerve, muscle,
including cardiac muscle, and other tissues and wounds, and organs such as liver, brain,
lung, cardiac, pancreas and kidney tissue. The proteins may also be useful for the induction
inhibition of growth and/or differentiation of undifferentiated embryonic and stem cells.
The proteins may be complexed with other proteins, particularly members of the transforming
growth factor-beta superfamily of proteins.

L7: Entry 16 of 24

File: USPT

Dec 8, 1998

DOCUMENT-IDENTIFIER: US 5846770 A
TITLE: DNA molecules encoding human chordin

BSPR:
It is expected that other species, particularly human, have DNA sequences homologous to human
chordin protein. The invention, therefore, includes methods for obtaining the DNA sequences
encoding human chordin protein, the DNA sequences obtained by those methods, and the human
protein encoded by those DNA sequences. This method entails utilizing the human chordin protein
nucleotide sequence or portions thereof to design probes to screen libraries for the
corresponding gene from other species or coding sequences or fragments thereof from using
standard techniques. Thus, the present invention may include DNA sequences from other species,
which are homologous to human chordin protein and can be obtained using the human chordin
sequence. The present invention may also include functional fragments of the human chordin
protein, and DNA sequences encoding such functional fragments, as well as functional fragments of
other related proteins. The ability of such a fragment to function is determinable by assay of
the protein in the biological assays described for the assay of the chordin protein; for example
the BMP binding assays described in the examples. A DNA sequence encoding the complete mature
human chordin protein (SEQ ID NO: 1 and SEQ ID NO: 2) and the corresponding amino acid sequence
(SEQ ID NO: 3) are set forth herein. The chordin proteins of the present invention, such as human
chordin, may be produced by culturing a cell transformed with the correlating DNA sequence, such
as the human chordin DNA sequence of SEQ ID NO: 2, and recovering and purifying protein, such as
human chordin, from the culture medium. The purified expressed protein is substantially free from
other proteinaceous materials with which it is co-produced, as well as from other contaminants.
The recovered purified protein is contemplated to have the ability to bind to BMPs and hence to
exhibit effects on cartilage, bone and/or other connective tissue formation activity. Thus, the
proteins of the invention may be further characterized by the ability to demonstrate effects on

cartilage, bone and/or other connective tissue formation activity in bone and cartilage formation
and other assays described below. Chordin proteins may be further characterized by the ability to
demonstrate effects upon the growth and/or differentiation of embryonic cells and/or stem cells.
Thus, the proteins or compositions of the present invention may also be characterized by their
ability to enhance, enrich or otherwise influence the growth and/or differentiation of the cells.

17. Document ID: US 5741641 A

L7: Entry 17 of 24
File: USPT
Apr 21, 1998

US-PAT-NO: 5741641
DOCUMENT-IDENTIFIER: US 5741641 A
TITLE: Morphogenic protein screening method
DATE-ISSUED: April 21, 1998

US-CL-CURRENT: 435/6; 435/7.1

APPL-NO: 8/ 451953
DATE FILED: May 26, 1995

PARENT-CASE:
This patent application is a continuation of U.S. Ser. No. 08/278,729, filed Jul. 20, 1994, which
is a continuation of U.S. Ser. No. 07/938,021, filed Aug. 28, 1992, abandoned; which is a
continuation-in-part of U.S. Ser. No. 07/752,861, filed Aug. 30, 1991, abandoned; and a
continuation-in-part of U.S. Ser. No. 07/752,764, filed August 30, 1991, abandoned, both of which
are a continuation-in-part of U.S. Ser. No. 07/667,274, filed Mar. 11, 1991, abandoned.

IN: Smart; John E., Oppermann; Hermann, Ozkaynak; Engin, Kuberasampath; Thangavel,
Rueger; David C., Pang; Roy H. L., Cohen; Charles M.

AB: Disclosed is a method of screening candidate compounds for the ability to
modulate the level of morphogenic protein in mammalian system. The method includes
determining a parameter indicative of the level of production of a morphogenic in a cell
culture known to produce the morphogen, incubating a candidate compound with the culture for
a time sufficient to allow the compound to affect the production of the morphogenic protein,
and then assaying the culture again to detect a change in the level of morphogenic protein
production.

L7: Entry 17 of 24
File: USPT
Apr 21, 1998

DOCUMENT-IDENTIFIER: US 5741641 A
TITLE: Morphogenic protein screening method

DEPR:
The invention is based on the discovery of a family of structurally related morphogenic proteins
(BMPs), also called osteogenic proteins (OPs), and more particularly that various of these
proteins play an important role, not only in embryogenesis, but also in tissue and organ
maintenance and repair in juvenile and adult mammals. Morphogenic proteins which have been
identified include BMP 2, 3, 4, 5, 6, OP-1 and OP-2 (murine and human), Vgr-1, Vgl, DPP, GDF-1,
CMBP-2A, CMBP-2B, 60A, and the inhibin/activin class of proteins. Other recombinant proteins
include COP1, COP3, COP4, COP5, COP7, and COP16. While, as explained herein, the morphogen have
significant homologies and similarities in structure, it is hypothesized that variants within the
morphogenic protein genes may have specific roles in specific tissue involving, for example,
stimulation of progenitor cell multiplication, tissue specific or tissue preferred phenotype
maintenance, and/or stimulation or modulation of the rate of differentiation, growth or
replication of tissue cells characterized by high turnover. The effect on the long-term
physiology, maintenance and repair of particular tissues by particular species of the morphogens
is currently unknown in any significant detail. However, methods useful in determining which
particular tissues express which particular morphogen(s), and for finding changes which stimulate
or depress morphogen expression in vivo, would enable discovery and development of strategies for
therapeutic treatment of a large number of diseased states, and provide drugs designed to
implement the strategy.

18. Document ID: US 5707810 A

L7: Entry 18 of 24
File: USPT
Jan 13, 1998

US-PAT-NO: 5707810
DOCUMENT-IDENTIFIER: US 5707810 A
TITLE: Method of diagnosing renal tissue damage or disease
DATE-ISSUED: January 13, 1998

US-CL-CURRENT: 435/6; 435/7.21

APPL-NO: 8/ 643563
DATE FILED: May 6, 1996

PARENT-CASE:
This patent application is a continuation of U.S. Ser. No. 08/278,729, filed Jul. 20, 1994, now
U.S. Pat. No. 5,650,276 which is a continuation of U.S. Ser. No. 07/938,021, filed Aug. 28, 1992,
abandoned, which is a continuation-in-part of U.S. Ser. No. 07/752,861, filed Aug. 30, 1991,
abandoned which is a continuation-in-part of U.S. Ser. No. 07/667,274, filed Mar. 11, 1991,
abandoned.

IN: Smart; John E., Oppermann; Hermann, Ozkaynak; Engin, Kuberasampath; Thangavel,
Rueger; David C., Pang; Roy H. L., Cohen; Charles M.

AB: In one aspect, the present invention provides a method of diagnosing renal tissue
damage or disease by measuring endogenous expression of OP-1 by renal tissue of a mammal
(e.g., a human) in which a depression of endogenous expression relative

to undamaged or
undiseased mammalian renal tissue indicates a diagnosis that the mammal is afflicted with
renal tissue damage or disease. Also disclosed are methods of diagnosing renal tissue damage
or disease in a mammal. The methods involve detecting and/or measuring the expression of the
OP-1 (BMP-7) gene or protein in the mammal. Depression of OP-1 expression may be used to
diagnose renal tissue damage or disease.

L7: Entry 18 of 24

File: USPT

Jan 13, 1998

DOCUMENT-IDENTIFIER: US 5707810 A
TITLE: Method of diagnosing renal tissue damage or disease

DEPR:
The invention is based on the discovery of a family of structurally related morphogenic proteins
(BMPs), also called osteogenic proteins (OPs), and more particularly that various of these
proteins play an important role, not only in embryogenesis, but also in tissue and organ
maintenance and repair in juvenile and adult mammals. Morphogenic proteins which have been
identified include BMP 2, 3, 4, 5, 6, OP-1 and OP-2 (murine and human), Vgr-1, Vgl, DPP, GDF-1,
CMBP-2A, CMBP-2B, 60A, and the inhibin/activin class of proteins. Other recombinant proteins
include COP1, COP3, COP4, COP5, COP7, and COP16. While, as explained herein, the morphogen have
significant homologies and similarities in structure, it is hypothesized that variants within the
morphogenic protein genes may have specific roles in specific tissue involving, for example,
stimulation of progenitor cell multiplication, tissue specific or tissue preferred phenotype
maintenance, and/or stimulation or modulation of the rate of differentiation, growth or
replication of tissue cells characterized by high turnover. The effect on the long-term
physiology, maintenance and repair of particular tissues by particular species of the morphogens
is currently unknown in any significant detail. However, methods useful in determining which
particular tissues express which particular morphogen(s), and for finding changes which stimulate
or depress morphogen expression in vivo, would enable discovery and development of strategies for
therapeutic treatment of a large number of diseased states, and provide drugs designed to
implement the strategy.

19. Document ID: US 5650276 A

L7: Entry 19 of 24

File: USPT

Jul 22, 1997

US-PAT-NO: 5650276
DOCUMENT-IDENTIFIER: US 5650276 A
TITLE: Morphogenic protein screening method
DATE-ISSUED: July 22, 1997

US-CL-CURRENT: 435/6; 435/29

APPL-NO: 8/ 278729
DATE FILED: July 20, 1994

PARENT-CASE:
This is a continuation of application Ser. No. 07/938,021 filed on Aug. 28, 1992, abandoned,
which is a continuation-in-part of U.S. Ser. No. 752,861, and U.S. Ser. No. 752,764, both filed
Aug. 30, 1991, both of which are continuations-in-part of U.S. Ser. No. 667,274, filed Mar. 11,
1991, the disclosures of each of which are incorporated herein by reference.

IN: Smart; John E., Oppermann; Hermann, Ozkaynak; Engin, Kuberasampath; Thangavel,
Rueger; David C., Pang; Roy H.L., Cohen; Charles M.

AB: Disclosed is a method of screening candidate compounds for the ability to
modulate the level of morphogenic protein in mammalian system. The method includes
determining a parameter indicative of the level of production of a morphogenic in a cell
culture known to produce the morphogen, incubating a candidate compound with the culture for
a time sufficient to allow the compound to affect the production of the morphogenic protein,
and then assaying the culture again to detect a change in the level of morphogenic protein
production.

L7: Entry 19 of 24

File: USPT

Jul 22, 1997

DOCUMENT-IDENTIFIER: US 5650276 A
TITLE: Morphogenic protein screening method

DEPR:
The invention is based on the discovery of a family of structurally related morphogenic proteins
(BMPs), also called osteogenic proteins (OPs), and more particularly that various of these
proteins play an important role, not only in embryogenesis, but also in tissue and organ
maintenance and repair in juvenile and adult mammals. Morphogenic proteins which have been
identified include BMP 2, 3, 4, 5, 6, OP-1 and OP-2 (murine and human), Vgr-1, Vgl, DPP, GDF-1,
CMBP-2A, CMBP-2B, 60A, and the inhibin/activin class of proteins. Other recombinant proteins
include COP1, COP3, COP4, COP5, COP7, and COP16. While, as explained herein, the morphogen have
significant homologies and similarities in structure, it is hypothesized that variants within the
morphogenic protein genes may have specific roles in specific tissue involving, for example,
stimulation of progenitor cell multiplication, tissue specific or tissue preferred phenotype
maintenance, and/or stimulation or modulation of the rate of differentiation, growth or
replication of tissue cells characterized by high turnover. The effect on the long-term
physiology, maintenance and repair of particular tissues by particular species of the morphogens
is currently unknown in any significant detail. However, methods useful in determining which
particular tissues express which particular morphogen(s), and for finding changes which stimulate
or depress morphogen expression in vivo, would enable discovery and development of strategies for
therapeutic treatment of a large number of diseased states, and provide drugs designed to
implement the strategy.

20. Document ID: US 5597897 A

L7: Entry 20 of 24
File: USPT
Jan 28, 1997

US-PAT-NO: 5597897
DOCUMENT-IDENTIFIER: US 5597897 A
TITLE: Pharmaceutical formulations of osteogenic proteins
DATE-ISSUED: January 28, 1997

US-CL-CURRENT: 530/350; 424/488, 530/399

APPL-NO: 8/ 081378
DATE FILED: June 29, 1993

PARENT-CASE:
This application is filed under 35 U.S.C. 371 as a national phase application of PCT/US92/05309,
as filed on Jun. 22, 1992, which claims priority from U.S. patent application Ser. No. 718,721,
filed on Jun. 21, 1991, now abandoned.

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/US92/05309	June 22, 1992	WO93/00050	Jan 7, 1993	Jun 29, 1993	Jun 29, 1993

IN: Ron; Eyal, Turek; Thomas J., Isaacs; Benjamin S., Patel; Himakshi, Kenley;
Richard A.

AB: A composition comprising a pharmaceutically acceptable admixture of an osteogenic
protein; a polymer matrix component selected from the group consisting of poly(lactic acid),
poly(glycolic acid), and copolymers of lactic acid and glycolic acid; and an osteogenic
protein-sequestering material.

L7: Entry 20 of 24
File: USPT
Jan 28, 1997

DOCUMENT-IDENTIFIER: US 5597897 A
TITLE: Pharmaceutical formulations of osteogenic proteins

DEPR:
The osteogenic proteins useful in the practice of the subject invention are well known to those
skilled in the art and include those discussed above. The preferred osteogenic proteins for use
herein are those of the BMP family identified as BMP-1 through BMP-8 in U.S. Pat. No. 4,877,864;
U.S. Pat. No. 5,013,649; WO 90/11366 published Oct. 4, 1990; and WO 91/18098 published Nov. 28,
1991. The most preferred is BMP-2, the mature protein sequence beginning with the amino acid Gln
at nucleotide 1202 and ending with the amino acid Arg at nucleotide 1543, as described in detail
in the '649 patent. Of course, combinations of two or more of such osteogenic proteins may be
used, as may fragments of such proteins that also exhibit osteogenic activity and heterodimeric
forms of such proteins. Recombinant proteins are preferred over naturally occurring isolated
proteins. The amount of osteogenic protein useful herein is that amount effective to stimulate
increased osteogenic activity of infiltrating progenitor cells, and will depend upon the size and
nature of the defect being treated as discussed in more detail below, such amounts being orders
of magnitude less than the amount of polymer matrix employed, preferably in the range of 1-50
.mu.g of protein for each 10 mg of polymer matrix employed and more preferably in the range of
0.5-5 .mu.g protein for each mg of polymer matrix employed.

21. Document ID: US 5520923 A

L7: Entry 21 of 24
File: USPT
May 28, 1996

US-PAT-NO: 5520923
DOCUMENT-IDENTIFIER: US 5520923 A
TITLE: Formulations for delivery of osteogenic proteins
DATE-ISSUED: May 28, 1996

US-CL-CURRENT: 424/426; 264/321, 528/495

APPL-NO: 8/ 308787
DATE FILED: September 19, 1994

IN: Tjia; Jane S., Kelley; Brian D., Northey; Richard P., Philbrook; C. Michael

AB: A formulation is disclosed comprising a pharmaceutically acceptable admixture of
an osteogenic protein and a sponge of porous particulate polymer matrix. The sponge may be
prepared by treating the porous particulate polymer matrix with a suitable fusing material
such as ethanol and a surfactant such as a polysorbate.

L7: Entry 21 of 24
File: USPT
May 28, 1996

DOCUMENT-IDENTIFIER: US 5520923 A
TITLE: Formulations for delivery of osteogenic proteins

DEPR:
The osteogenic proteins useful with the fused sponges made in accordance with the subject
invention are well known to those skilled in the art and include those discussed above. The
preferred osteogenic proteins for use herein are those of the BMP class identified as BMP-1
through BMP-12 in U.S. Pat. Nos. 4,877,864; 5,013,649; WO 90/11366 published Oct. 4, 1990; WO
91/18098 published Nov. 28, 1991; WO 93/00432, published Jan. 7, 1993; U.S. Ser. Nos. 08/247,908
and 08/247,904, both filed May 20, 1994; and U.S. Ser. No. 08/217,780,

filed on Mar. 25, 1994.
The disclosure of the above publications are hereby incorporated by reference. The most preferred
is BMP-2, the full length cDNA sequence of which is described in detail in the '649 patent. Of
course, combinations of two or more of such osteogenic proteins may be used, as may fragments of
such proteins that also exhibit osteogenic activity. Such osteogenic proteins are known to be
homodimeric species, but also exhibit activity as mixed heterodimers. Heterodimeric forms of
osteogenic proteins may also be used in the practice of the subject invention. BMP heterodimers
are described in WO93/09229, the disclosure of which is hereby incorporated by reference.
Recombinant proteins are preferred over naturally occurring isolated proteins. The amount of
osteogenic protein useful herein is that amount effective to stimulate increased osteogenic
activity of infiltrating progenitor cells, and will depend upon the size and nature of defect
being treated as discussed in more detail below, such amounts being orders of magnitude less than
the amount of porous particulate polymer matrix employed, generally in the range of 1-50 .mu.g of
protein for each 10 mg of fused sponge employed and more preferably in the range of 0.5-10 .mu.g
protein for each milligram of fused sponge employed (assuming approximately 0.2 g/cc density).

22. Document ID: US 5385887 A

L7: Entry 22 of 24
File: USPT
Jan 31, 1995

US-PAT-NO: 5385887
DOCUMENT-IDENTIFIER: US 5385887 A
TITLE: Formulations for delivery of osteogenic proteins
DATE-ISSUED: January 31, 1995

US-CL-CURRENT: 514/12; 106/645, 424/423, 424/426, 514/21, 514/8, 530/350, 530/397, 530/399,
530/840

APPL-NO: 8/ 119772
DATE FILED: September 10, 1993

IN: Yim; Kalvin W. K., Huberty; Michael C., Northey, Jr.; Richard P., Schrier; Jay A.

AB: A composition is disclosed comprising a pharmaceutically acceptable admixture of
an osteogenic protein; a porous particulate polymer matrix; an osteogenic
protein-sequestering amount of blood clot; and a calcium sulfate hemihydrate-containing
substance. Also disclosed are formulations of bone morphogenetic proteins with improved
solubility and/or stability characteristics.

L7: Entry 22 of 24
File: USPT
Jan 31, 1995

DOCUMENT-IDENTIFIER: US 5385887 A
TITLE: Formulations for delivery of osteogenic proteins

BSPR:
The osteogenic proteins useful in the practice of the subject invention are well known to those
skilled in the art and include those discussed above. The preferred osteogenic proteins for use
herein are those of the BMP class identified as BMP-1 through BMP-10 in U.S. Pat. No. 4,877,864;
U.S. Pat. No. 5,013,649; WO 90/11366 published Oct. 4, 1990; WO 91/18098 published Nov. 28, 1991;
WO 93/00432, published Jan. 7, 1993 and U.S. Ser. No. 08/061,695, filed May 12, 1993. The
disclosure of the above publications are hereby incorporated by reference. The most preferred is
BMP-2, the full length cDNA sequence of which is described in detail in the '649 patent. Of
course, combinations of two or more of such osteogenic proteins may be used, as may fragments of
such proteins that also exhibit osteogenic activity. Such osteogenic proteins are known to be
homodimeric species, but also exhibit activity as mixed heterodimers. Heterodimeric forms of
osteogenic proteins may also be used in the practice of the subject invention. BMP heterodimers
are described in WO93/09229, the disclosure of which is hereby incorporated by reference.
Recombinant proteins are preferred over naturally occurring isolated proteins. The amount of
osteogenic protein useful herein is that amount effective to stimulate increased osteogenic
activity of infiltrating progenitor cells, and will depend upon the size and nature of defect
being treated as discussed in more detail below, such amounts being orders of magnitude less than
the amount of porous particulate polymer matrix employed, generally in the range of 1-50 .mu.g of
protein for each 10 mg of porous particulate polymer matrix employed and more preferably in the
range of 0.5-10 .mu.g protein for each milligram of polymer matrix employed (assuming 0.2 g/cc
density).

23. Document ID: US 5171579 A

L7: Entry 23 of 24
File: USPT
Dec 15, 1992

US-PAT-NO: 5171579
DOCUMENT-IDENTIFIER: US 5171579 A
TITLE: Formulations of blood clot-polymer matrix for delivery of osteogenic proteins
DATE-ISSUED: December 15, 1992

US-CL-CURRENT: 424/486; 424/484

APPL-NO: 7/ 776514
DATE FILED: October 11, 1991

IN: Ron; Eyal, Schaub; Robert G., Turek; Thomas J.

AB: A composition comprising a pharmaceutically acceptable admixture of an osteogenic
protein; a porous particulate polymer matrix; and an osteogenic protein-sequestering amount
of blood clot.

L7: Entry 23 of 24
File: USPT
Dec 15, 1992

DOCUMENT-IDENTIFIER: US 5171579 A
TITLE: Formulations of blood clot-polymer matrix for delivery of osteogenic proteins

DEPR:
The osteogenic proteins useful in the practice of the subject invention are well known to those
skilled in the art and include those discussed above. The preferred osteogenic proteins for use
herein are those of the BMP class identified as BMP-1 through BMP-8 in U.S. Pat. No. 4,877,864;
U.S. Pat. No. 5,013,649; copending U.S. patent applications Ser. No. 437,409, aband. Ser. No.
490,033, and Ser. No. 438,919 (all three WO 90/11366 published Oct. 4, 1990); and Ser. No.
525,357. All references cited herein are hereby incorporated by reference. The most preferred is
BMP-2, the full length cDNA sequence and the ultimate mature protein sequence described in detail
in the '649 patent. Of course, combinations of two or more of such osteogenic proteins may be
used, as may fragments of such proteins that also exhibit osteogenic activity. Such osteogenic
proteins are known to be homodimeric species, but also exhibit activity as mixed heterodimers.
Recombinant proteins are preferred over naturally occurring isolated proteins. The amount of
osteogenic protein useful herein is that amount effective to stimulate increased osteogenic
activity of infiltrating progenitor cells, and will depend upon the size and nature of defect
being treated as discussed in more detail below, such amounts being orders of magnitude less than
the amount of polymer matrix employed, generally in the range of 1-30 .mu.g of protein for each
10 mg of polymer matrix employed.

24. Document ID: EP 1100872 A1, WO 200005344 A1, AU 9951242 A

L7: Entry 24 of 24 File: DWPI May 23, 2001

DERWENT-ACC-NO: 2000-171427
DERWENT-WEEK: 200130

TITLE: Maintaining Drosophila germline stem cells, useful for developing methods for treating
e.g. tumors, infertility, hematologic conditions, wounds, aging or damaged or diseased tissues

PRIORITY-DATA: 1998US-0094008 (July 24, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1100872 A1	May 23, 2001	E	000	C12N005/02
WO 200005344 A1	February 3, 2000	E	040	C12N005/02
AU 9951242 A	February 14, 2000	N/A	000	C12N005/02

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
EP 1100872A1	July 23, 1999	1999EP-0935857	N/A
EP 1100872A1	July 23, 1999	1999WO-US16633	N/A
EP 1100872A1		WO 200005344	Based on
WO 200005344A1	July 23, 1999	1999WO-US16633	N/A
AU 9951242A	July 23, 1999	1999AU-0051242	N/A
AU 9951242A		WO 200005344	Based on

INT-CL (IPC): C12N 5/02; C12N 5/06
IN: SPRADLING, A C, XIE, T

AB: NOVELTY - A method for maintaining germline stem cells of Drosophila
comprises providing a population of the germline stem cells, and stimulating signal
transduction by a bone morphogenic protein (BMP) signaling pathway in at least one
cell of the population, the stimulation maintains more germline stem cells in the
population compared to a population which has not had the signal transduction.,
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:, (1) a
cell population made by the novel method, where there are at least 10 germline stem
cells in the population for each germline stem cell present prior to stimulation of
BMP signaling;, (2) a method for maintaining Drosophila stem cells comprising
providing a population comprised of the stem cells, and stimulating decapentaplegic
(dpp) signaling such that more stem cells of the population are maintained as at least
viable or undifferentiated as compared to a population of stem cells which has not
been stimulated;, (3) a method of reducing or eliminating stem cells or tumor cells of
an organism comprising regressing signal transduction by a BMP receptor pathway such
that the stem cells or tumor cells are reduced or eliminated;, (4) a method of
increasing abundance of stem cells of an organism comprising stimulating signal
transduction by a BMP receptor pathway such that abundance of at least some stem cells
is increased;, (5) a method of increasing lifetime of stem cells of an organism

comprising stimulating signal transduction by a BMP receptor pathway such that the
lifetime of at least some stem cells in increased., ACTIVITY - Vulnery; cytostatic.,
MECHANISM OF ACTION - Bone morphogenetic protein modulator., USE - The methods can be
used for maintaining or propagating Drosophila stem cells in vivo or in vitro. Using
the methods, it is possible to extend the life span of stem cells. Drugs that
upregulate BMP signaling to stem cells may enhance fertility in humans and animals,
such as male fertility in patients with reduced numbers of germline stem cells (basal
cells). Such drugs may ameliorate hematologic conditions caused by reduced stem cell
functioning, e.g. aplastic anemias, agammaglobulinemia, and related conditions. Drugs
enhancing BMP signaling may enhance wound healing. Aging-related pathologies caused by
loss of stem cells, such as hair loss, loss of muscle mass, reduction of blood cell
numbers, and the aging of the skin and other stem cell-dependent tissues could be
treated by increasing BMP signal transduction. Compounds enhancing BMP signaling may
increase the average lifespan of an organism. Drugs inhibiting BMP signaling pathways
may be useful therapies against teratocarcinoma by causing stem cell differentiation,
e.g. drugs which inhibit BMP signaling may be successful treatments against ovarian
germline tumors dependent upon BMP signaling for continued growth. Increased or
decreased BMP signaling to stem cells might allow populations of stem cells to expand
prior to bone marrow transplant, increasing the chances of successful transplantation
and reducing the amount of donor marrow required. Further, control of BMP signaling
pathways may permit stem cells other than those in bone marrow to be removed from a
patient, expanded in vitro, and subsequently reintroduced into the patient to repair
tissues damaged by injury or disease, such as Parkinson's disease. Bone marrow from
patients with hematologic tumors, such as lymphoma and leukemia, could be tested for
BMP sensitivity. Positive test results for BMP sensitivity would allow steps to be
taken to avoid potential side effects of anti-BMP treatment in vivo, e.g. marrow
removed from the patient could be cleansed of tumors cells by inhibiting BMP
signaling, thereby inducing differentiation of tumor cells and reducing the tumor
burden. The cleansed marrow would subsequently be returned to the patient in an
autologous bone marrow transplant. Such differentiation therapy could also be used for
solid tumors e.g. sarcoma, carcinoma, and neuroglioma to reduce tumor burden. Therapy
may be used alone or in association with other treatments e.g. chemotherapy,
hyperthermia, or radiation, which preferentially kills rapidly dividing cells and
surgical resection of tumor. The methods can provide a model of ovarian tumor
formation in which overexpression of dpp produces ovarian stem cell tumors. In
addition, one or more genes of the stem cell may be activated or inhibited by chemical
or environmental induction, antisense, ribozyme, chimeric repair vector, RNAi, or
random/sequence-specific insertion. Ectopic expression of a gene may be controlled in
a particular spatial or temporal manner, mimic pathologic or disease states, or create
phenocopies of mutations in the endogenous gene. The methods can also be used in
agriculture and wildlife conservation.

L7: Entry 24 of 24

File: DWPI

May 23, 2001

DERWENT-ACC-NO: 2000-171427
DERWENT-WEEK: 200130

TITLE: Maintaining Drosophila germline stem cells, useful for developing methods for
treating e.g. tumors, infertility, hematologic conditions, wounds, aging or damaged or
diseased tissues

ABTX :
NOVELTY - A method for maintaining germline stem cells of Drosophila comprises providing a
population of the germline stem cells, and stimulating signal transduction by a bone
morphogenic protein (BMP) signaling pathway in at least one cell of the population, the
stimulation maintains more germline stem cells in the population compared to a population
which has not had the signal transduction.

ABTX:
(3) a method of reducing or eliminating stem cells or tumor cells of an organism comprising
regressing signal transduction by a BMP receptor pathway such that the stem cells or tumor
cells are reduced or eliminated;

ABTX:
(4) a method of increasing abundance of stem cells of an organism comprising stimulating
signal transduction by a BMP receptor pathway such that abundance of at least some stem
cells is increased;

ABTX:
(5) a method of increasing lifetime of stem cells of an organism comprising stimulating
signal transduction by a BMP receptor pathway such that the lifetime of at least some stem
cells in increased.

ABTX:
USE - The methods can be used for maintaining or propagating Drosophila stem cells in vivo
or in vitro. Using the methods, it is possible to extend the life span of stem cells. Drugs
that upregulate BMP signaling to stem cells may enhance fertility in humans and animals,
such as male fertility in patients with reduced numbers of germline stem cells (basal
cells). Such drugs may ameliorate hematologic conditions caused by reduced stem cell
functioning, e.g. aplastic anemias, agammaglobulinemia, and related conditions. Drugs
enhancing BMP signaling may enhance wound healing. Aging-related pathologies caused by loss
of stem cells, such as hair loss, loss of muscle mass, reduction of blood cell numbers, and
the aging of the skin and other stem cell-dependent tissues could be treated by increasing
BMP signal transduction. Compounds enhancing BMP signaling may increase the average
lifespan of an organism. Drugs inhibiting BMP signaling pathways may be useful therapies
against teratocarcinoma by causing stem cell differentiation, e.g. drugs which inhibit BMP
signaling may be successful treatments against ovarian germline tumors

dependent upon BMP
signaling for continued growth. Increased or decreased BMP signaling to stem cells might
allow populations of stem cells to expand prior to bone marrow transplant, increasing the
chances of successful transplantation and reducing the amount of donor marrow required.
Further, control of BMP signaling pathways may permit stem cells other than those in bone
marrow to be removed from a patient, expanded in vitro, and subsequently reintroduced into
the patient to repair tissues damaged by injury or disease, such as Parkinson's disease.
Bone marrow from patients with hematologic tumors, such as lymphoma and leukemia, could be
tested for BMP sensitivity. Positive test results for BMP sensitivity would allow steps to
be taken to avoid potential side effects of anti-BMP treatment in vivo, e.g. marrow removed
from the patient could be cleansed of tumors cells by inhibiting BMP signaling, thereby
inducing differentiation of tumor cells and reducing the tumor burden. The cleansed marrow
would subsequently be returned to the patient in an autologous bone marrow transplant. Such
differentiation therapy could also be used for solid tumors e.g. sarcoma, carcinoma, and
neuroglioma to reduce tumor burden. Therapy may be used alone or in association with other
treatments e.g. chemotherapy, hyperthermia, or radiation, which preferentially kills
rapidly dividing cells and surgical resection of tumor. The methods can provide a model of
ovarian tumor formation in which overexpression of dpp produces ovarian stem cell tumors.
In addition, one or more genes of the stem cell may be activated or inhibited by chemical
or environmental induction, antisense, ribozyme, chimeric repair vector, RNAi, or
random/sequence-specific insertion. Ectopic expression of a gene may be controlled in a
particular spatial or temporal manner, mimic pathologic or disease states, or create
phenocopies of mutations in the endogenous gene. The methods can also be used in
agriculture and wildlife conservation.